TOTAL SYNTHESIS OF AGROCHEMICALLY RELEVANT NATURAL PRODUCTS AND ITS ANALOGUES

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Introduction

Heterocyclic compounds are constituted with different heteroatoms that enable unique physicochemical properties and structural features that empower them to interact with different biological systems *via H*-bonding that could lead to the biological activity. Compounds with heterocycles are important structural motifs found in natural products and diverse biologically active compounds possessing pharmacological (antifungal, antibacterial, anticonvulsant, anti-inflammatory, anti-viral, analgesic, antitumor to anticancer abilities)[1] as well as agrochemical (insecticide, fungicide and herbicide) activities[2]. Various heterocyclic ring systems are available, which include cyclic (simple and fused) and spiro compounds.

Heterocycles have inhabited one of the vast areas of research in organic chemistry for more than a century. Among them, *N*-*N* and *N*-*O* bond containing heterocyclic compounds have grabbed the interest of researchers due to their versatile structural features leading to biologically active motifs. Because of the extensive versatility, the synthesis of heterocyclic compounds has always been among the most important research areas in synthetic organic chemistry. In many areas, the classic methodology provides reliable access to heterocyclic compounds; however, they are no longer acceptable by current economical, safety and environmental standards which includes:

1. Fewer toxic reagents
2. Less harsh reaction conditions
3. Minimizing waste generation
4. Yield/cost efficient process

In order to address these challenges, advance of effective methodologies are essential in the field of organic synthesis. In this background, the present research work has been aimed to develop novel routes to heterocyclic compounds *via* different methodology's and to additionally evaluate their biological application in agroscience. All the new compounds thus synthesized were well characterized with the help of NMR, IR, and HRMS analysis. Finally, the biological activity of the synthesized molecules was investigated in crop-protection field.

Fused *N,N*-bridge containing heterocycles are important substructures found in numerous natural products and synthetic alkaloids.[1] The importance of fused *N,N*-bridged heterocycles have appeared owing to their wide variety of biological activities have motivated research aimed at the development of new economical, efficient, and selective synthetic strategies to access these compounds. Azomethine imines of pyrazolidin-3-one have been widely used for [3+2] cycloaddition reactions with alkynes and alkenes to form heterocycles. In cycloaddition reactions donor–acceptor substituted cyclopropanes have emerged as versatile 1,3 dipolar building blocks. In the **first chapter, we have set objectives and aimed for the novel methodology to synthesize fused *N,N*-bridge heterocyclic compounds** from 1,3 dipoles of substituted cyclopropane and azomethine imines of pyrazoline-3-one.

Isooxazolines are five-membered nitrogen and oxygen-containing heterocycles that constitute an important structural component of a diverse range of biologically active natural compounds and pharmaceuticals. In principle, such ring systems can be constructed by different approaches: cycloadditions, condensation, and intramolecular cyclization. Still, the synthesis of 5,5-dimethyl-isoxazolines suffers from greater challenges with limited available synthetic methods. The development of new strategies for the synthesis of functionalized isoxazolines has remained highly attractive but challenging. The **second chapter we have has set the objective and aimed for novel synthetic methods for the synthesis of functionalized isoxazolines** in a highly efficient manner.

In the **third chapter,** we aimed to test all compounds against all three agrochemical indications (insecticide, fungicide, and herbicide).

The thesis entitled "**Total Synthesis of Agrochemically Relevant Natural Products and its Analogues**" has been divided into the following three chapters.

Chapter 1

Development of Novel Methodology For Synthesizing *N,N*-Fused Heterocyclic Compounds *Via* Lewis Acid-Mediated 1,3-Dipolar Cycloaddition of *N,N*-Cyclic Azomethine Imine With Donor-Acceptor Cyclopropanes

1.1: Brief review on *N,N* bridge fused heterocyclic compounds, their applications and methods to synthesize those compounds.

Chapter 1.1 deals with a brief review of *N,N*-fused heterocyclic compounds, and the applications and methods available to synthesize those compounds.

Heterocycles with an *N,N*-bridge are important structural motifs found in diverse biologically active compounds (**Figure 1**).[1] One of them (pinoxaden) is commercially used as an agrochemical for herbicidal applications and several such nitrogen-containing fused heterocycles have shown herbicidal activity.[2] Bicyclic pyrazolone motifs, as depicted in **Figure 1**, have also shown a range of other diverse biological activities, such as antibacterial, TNF-α modulator (tumor necrosis factor), and calcitonin receptor agonist action. 5,5-fused *N,N*-bridge bicyclic and 5,6-fused *N,N*-bridge bicyclic represent a promising chemical area for the development of new drugs to combat different life-threatening diseases as well as for the development of new agrochemical active ingredients.[1]

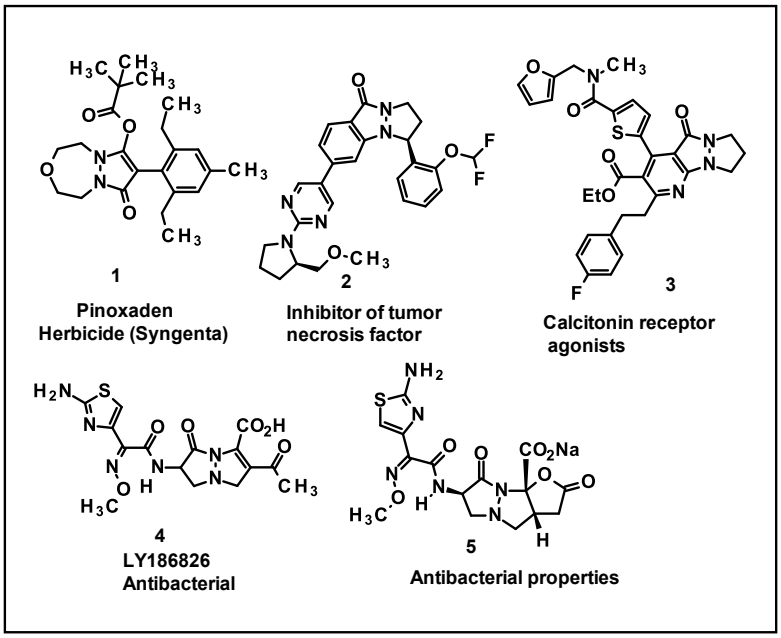


Figure 1: Biologically active fused *N,N*-bridge heterocycles

1.2: Brief review on Azomethine imines of pyrazolidin-3-one and their applications in cycloaddition reactions

Chapter 1.2 deals with a brief review on the synthesis and applications of azomethine imines of pyrazolidin-3-one in cycloaddition reactions.

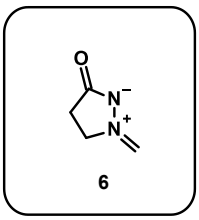


Figure 2: Azomethine imines of pyrazolidin-3-one

Cycloaddition reactions are a powerful approach and have been well utilized for the construction of such heterocycles *via* concerted or ionic mechanisms in C–C bond forming reactions. Azomethine imines of pyrazolidin-3-one have been widely used for [3+2] cycloaddition reactions with alkynes and alkenes to form heterocycles.[3] Both thermal as well as copper-catalyzed cycloaddition reactions of pyrazolidin-3-one azomethine imine with alkynes have been reported in the literature and are well explored.[4] Shibata *et al.* have also reported a 1,3-dipolar cycloaddition reaction of azomethine imine with trifluoromethyl acrylates.[5] There is also a report by Chen *et al.* on a gold-catalyzed [3+2] cycloaddition reaction with allenes.[6] Several research groups have also reported [3+3] cycloaddition reactions of azomethine imines. The Huang,[7] Schmalz,[8] Hayashi,[9] Toste,[10] and Scheidt[11] groups have reported different methodologies for [3+3] cycloaddition reactions employing pyrazolidin-3-one imines.

1.3: Introduction on Donor–acceptor substituted cyclopropanes and its synthesis and applications in cycloaddition reactions

Chapter 1.3 deals with a brief review on donor–acceptor substituted cyclopropanes and their applications in cycloaddition reaction.

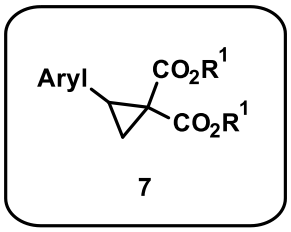


Figure 3: Donor–acceptor substituted cyclopropanes

Donor–acceptor substituted cyclopropanes have emerged as versatile building blocks for the construction of acyclic, cyclic, and heterocyclic scaffolds.[12–15] Charette and co-workers have reported[16] a cycloaddition reaction of donor–acceptor substituted cyclopropanes with quinoline azomethine imines and isoquinoline azomethine imines. Tang and co-workers[17] have also reported an enantioselective asymmetric [3+3] cycloaddition of donor–acceptor substituted cyclopropane diesters with aromatic azomethine.

1.4: Research objective.

Chapter 1.4 deals with the research objective

In the first chapter, it was aimed and set the objective to develop a novel methodology for synthesizing 5,5-fused *N,N*-bridge bicyclic, 5,6-fused *N,N*-bridge bicyclic compounds, and 5,5,5-fused *N,N*-bridge tricyclic compounds *via* Lewis acid-mediated [3+2] and [3+2] cycloaddition of *N,N*-cyclic azomethine imine with donor-acceptor cyclopropanes

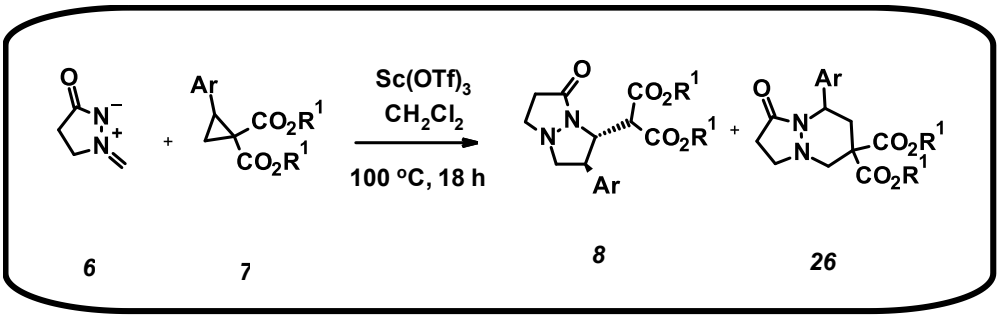
To the best of our knowledge, cycloaddition reactions of donor–acceptor cyclopropanes with the combination of an azomethine imine of pyrazolidin- 3-one has not been reported in the literature before. Therefore, our objective was to establish methodologies for both [3+2] and [3+3] cycloaddition reactions using a 1,3-dipolar

system comprising donor-acceptor cyclopropane diesters and pyrazolidin-3-one imine in the presence of a Lewis acid. This approach holds the potential for synthesizing unprecedented and novel 5,5-fused *N,N*-bridge bicyclic compounds, 5,6-fused *N,N*-bridge bicyclic compounds and 5,5,5-fused *N,N*-bridge tricyclic compounds.

1.5. Development of novel methodologies for the synthesis of 5,5-fused *N,N*-bridge bicyclic compounds via Lewis acid-mediated 1,3-dipolar cycloaddition of *N,N*-cyclic azomethine imine with donor-acceptor cyclopropanes.

Chapter 1.5 deals with strategic plan to develop novel methodology to synthesize 5,5-fused *N,N*-bridge bicyclic compounds.

We started the exploration of different Lewis acids (LAs) and solvents (**Table 1**) for [3+2] cycloaddition reaction of donor–acceptor cyclopropanes with the combination of an azomethine imine of pyrazolidin-3-one. We were amazed in finding the selectivity towards the 5,5-fused *N,N*-bridge bicyclic compounds in the cycloaddition reaction. The optimum condition for [3+2] cycloaddition reaction was found to be 0.20 mmol of cyclopropyl compound **7**, 0.40 mmol of azomethine imine **6** in DCE (2 mL) and 30 mol% of $Sc(OTf)_3$ under seal tube condition at 100 °C for 18 h. We have developed the methodology and applied it to synthesize 5,5-fused *N,N*-bridge bicyclic compounds and the substrate scope is depicted in the below table.



Scheme 1: [3+2] cycloaddition reactions of azoemthine imine with donar-acceptor cyclopropanes

The reaction proceeds in better yields with cyclopropanes that are substituted with electron-donating substituents (**Table -1**, compounds **8, 9, 11**). Donor–acceptor cyclopropanes with *ortho*-substituted phenyl rings, *e.g.,* substituted with methoxy or

methyl groups, react under these conditions to form mixtures of [3+2] and [3+3] cyclo addition products (**12**/**30** and **13**/**31**) in lower yields. The reaction proceeds in low yields for cyclopropyl substrates which do not have electron-donating substituents on the thiophene (**14**).

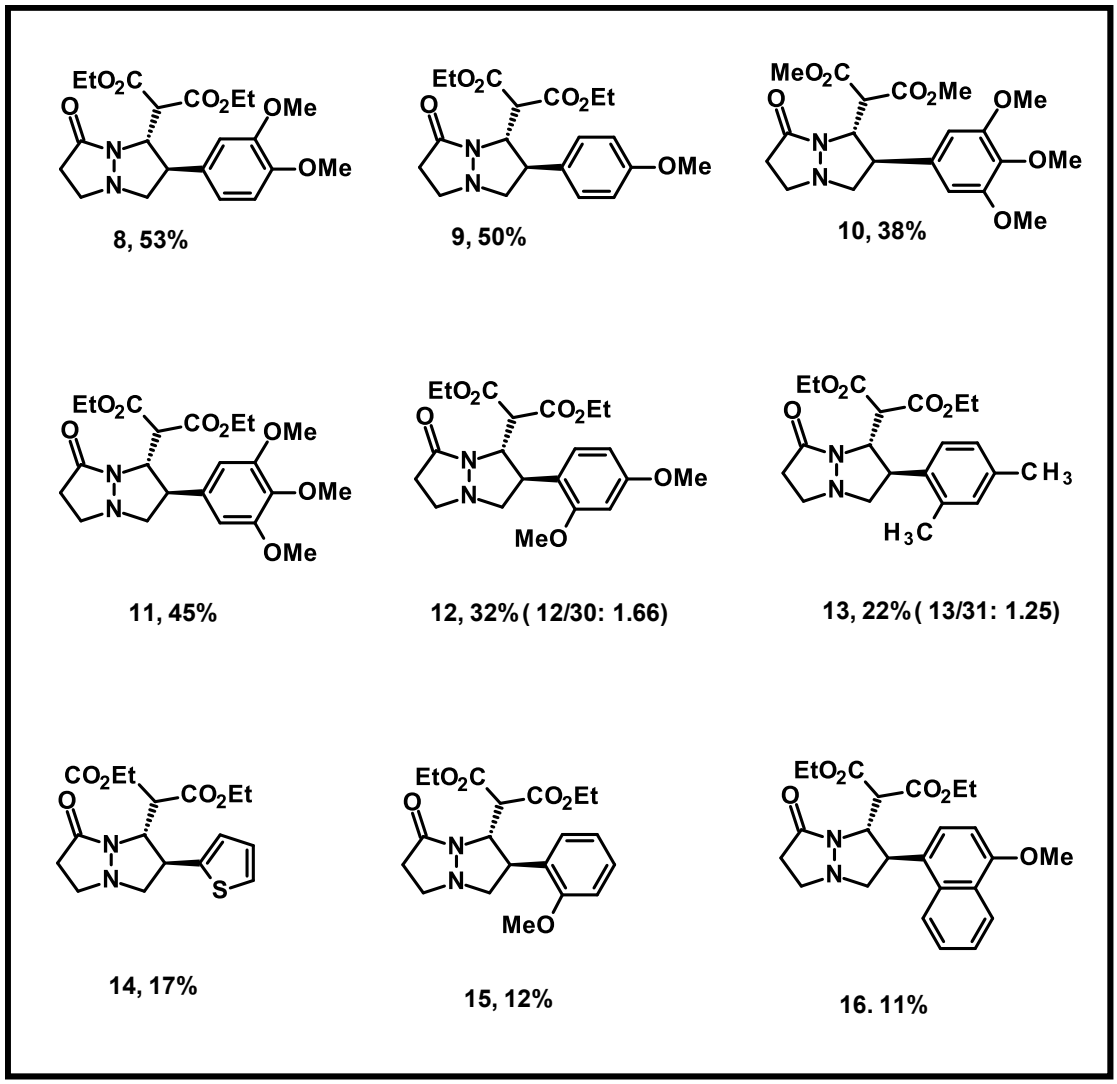
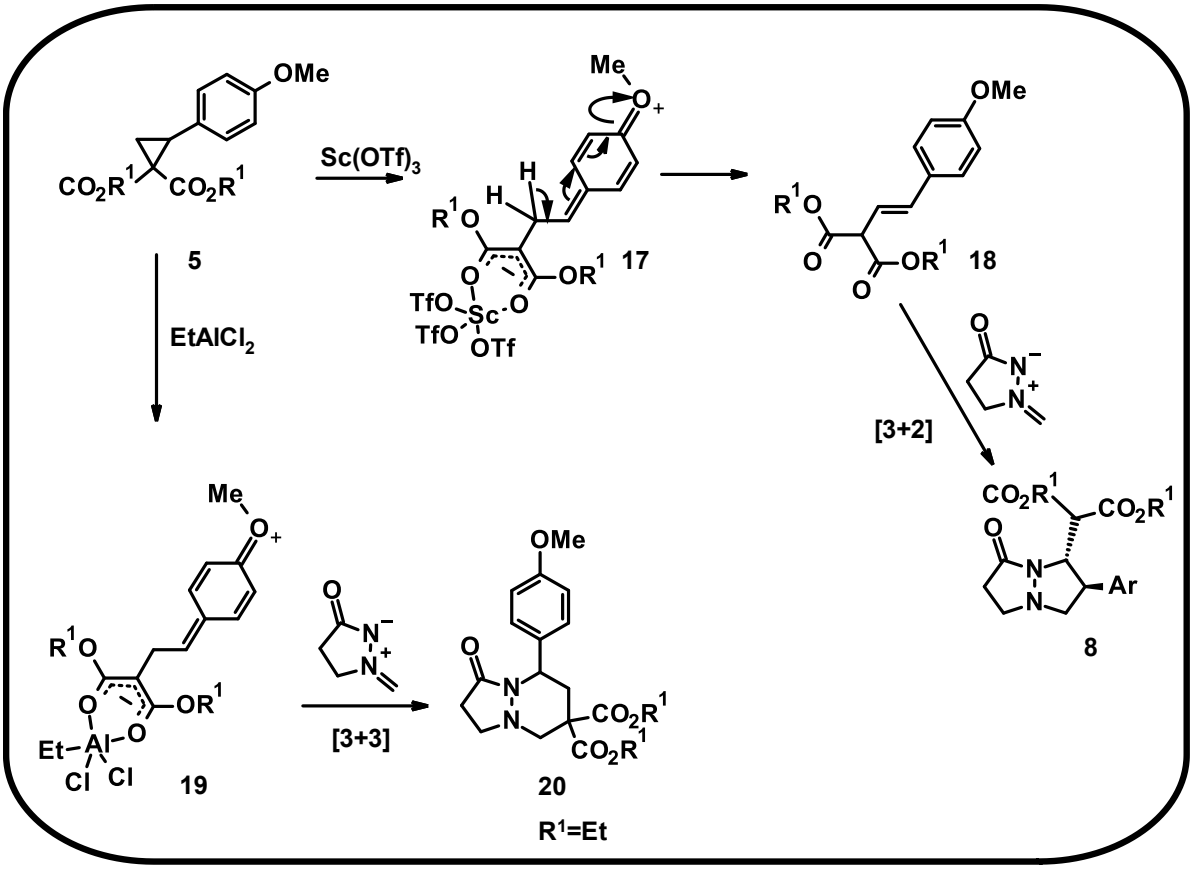


Table 1: 5,5-fused *N,N*-bridge bicyclic compounds

We proposed the following mechanism for the two cycloadditions reactions described above (Scheme 2). Scandium (III) triflate reacts with the donor–acceptor cyclopropane to form 1,3-zwitterionic species **17**, which undergoes hydride elimination and subsequent protonation or *via* 1,2-hydride shift, to form unsaturated

diester **18**. Intermediate **18** then undergoes a 1,3-dipolar cycloaddition reaction with the azomethine **6** imine to form 5,5-fused heterocycle **8**.



Scheme 2: Mechanism of the [3+2] and [3+3] cycloadditions reactions of azomethine imine with donor-acceptor cyclopropanes

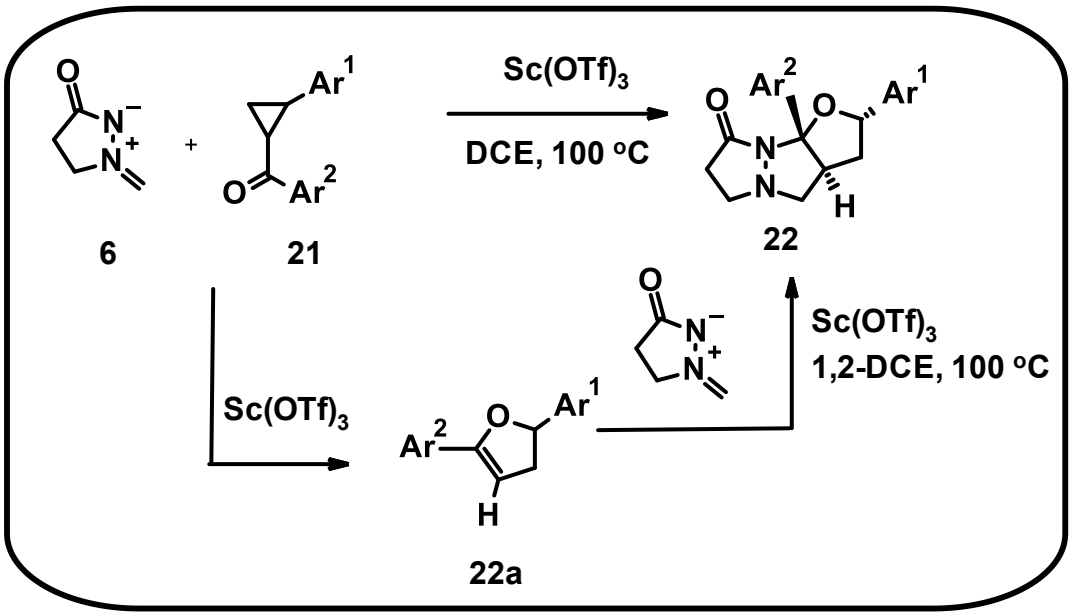
1.6: Development of novel methodologies for the synthesis of 5,5,5-fused *N,N*-bridge tricyclic compounds via Lewis acid-mediated 1,3-dipolar cycloaddition of *N,N*-cyclic azomethine imine with donor-acceptor cyclopropanes.

Chapter 1.6 deals with a strategic plan to develop a novel methodology to synthesize 5,5,5-fused *N,N*-bridge tricyclic compounds.

Donor–acceptor cyclopropanes containing aryl carbonyl **21** as the EWG react with azomethine imine **6** in the presence of $Sc(OTf)_3$ to form tricyclic heterocycles in high

regioselectivity and high diastereoselectivity (**Scheme 3**). The reaction presumably proceeds *via* Sc (III) catalyzed rearrangement of cyclopropyl ketone to form dihydrofuran **22a** (Scheme 3), which subsequently undergoes a [3+2] cycloaddition reaction with azomethine imine **6** to form the 5,5,5-fused *N,N*-bridge tricyclic compound **22.**

We were surprised in finding the selectivity toward the 5,5,5-fused *N,N*-bridge tricyclic compound. The optimum condition for the cycloaddition reactions was found to be 0.20 mmol of cyclopropyl compound **21**, 0.40 mmol of azomethine imine **6** in anhydrous DCE (2 mL) and 30 mol% of $Sc(OTf)_3$ under seal tube condition at 100 °C for 18 h. We have applied this methodology to synthesize 5,5,5-fused *N,N*-bridge tricyclic compound, and substrate scope was mentioned below (**Table 2)**.



Scheme 3: [3+2] cycloadditions reactions of azomethine imine and donor-acceptor cyclopropanes

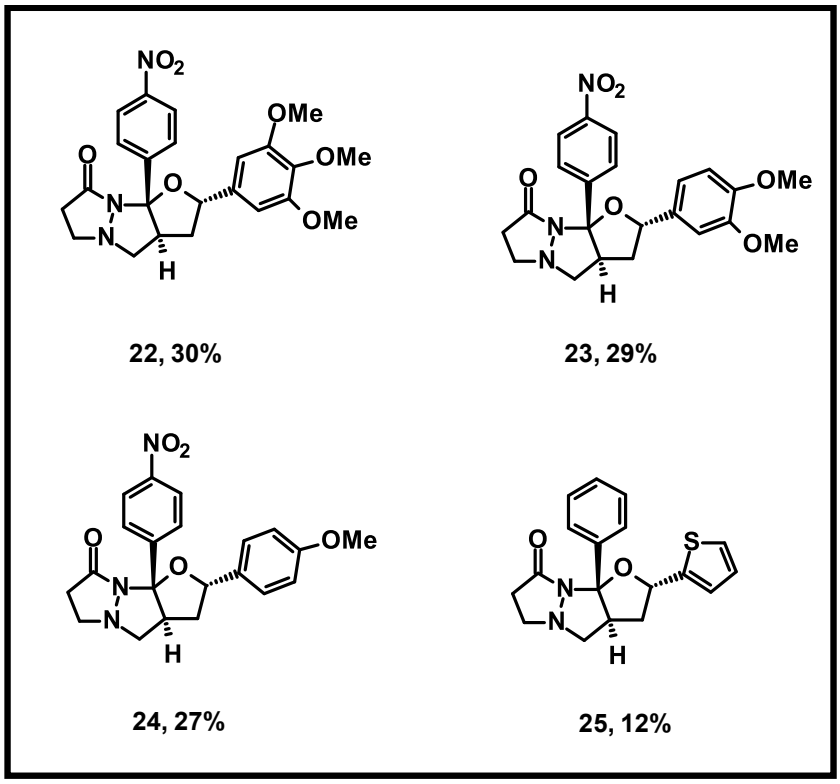
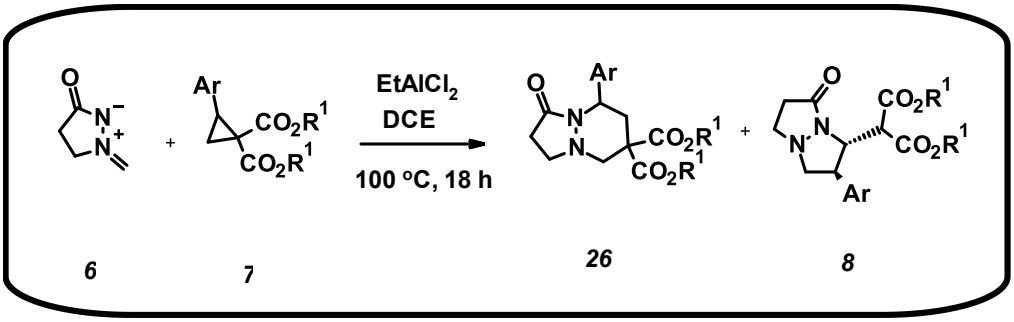


Table 2: 5,5,5-fused *N,N*-bridge tricyclic compounds

1.7: Development of novel methodologies for the synthesis of 5,6-fused *N,N*-bridge bicyclic compounds via Lewis acid-mediated 1,3-dipolar cycloaddition of *N,N*-cyclic azomethine imine with donor-acceptor cyclopropanes.

Section seven deals with strategic plan to develop novel methodology to synthesize 5,6-fused *N,N*-bridge bicyclic compounds.

We next looked into the use of the organometallic Lewis acid $EtAlCl_2$, which has been utilized by Tomilov *et al.* in the ring cleavage reaction of donor–acceptor cyclopropanes with 4,5-diazaspiro[2.4]hept-4-enes.[18] In fact, we were surprised to find that the use of $EtAlCl_2$ as a Lewis acid led to a complete divergence in the selectivity of the cycloaddition reaction (**Scheme 4**). The reaction of azomethine imine **6** and cyclopropane **7** in the presence of $EtAlCl_2$ (2.0 equiv) in DCM at 0 °C led to the formation of the [3+3] cycloaddition adduct in 38% yield (**entry 26**).



Scheme 4: [3+3] cycloaddition reactions of azomethine imine with donor-acceptor cyclopropanes

Complementary to the above Sc(III) mediated cycloaddition reactions, $EtAlCl_2$ effects the [3+3] cycloaddition reaction of donor–acceptor cyclopropanes **7** with dipolar azomethine imine **6** to form 5,6-fused *N,N*-bridge bicyclic compound **26** in high regioselectivity (Scheme 4). The reaction proceeds in lower yields and poor selectivity towards [3+3] versus [3+2] cycloaddition for substrates containing *ortho*-substituted aryl rings and also for substrates that are not activated by electron-donating substituents on the aryl ring **(Table 3, entry 30, 31, 32 & 34)**. $EtAlCl_2$, on the other hand, can form a stable 1,3-zwitterionic species **19**, which undergoes a [3+3] cycloaddition reaction with the azomethine imine **6** to form 5,6-fused *N,N*-bridge bicyclic compound **26**.

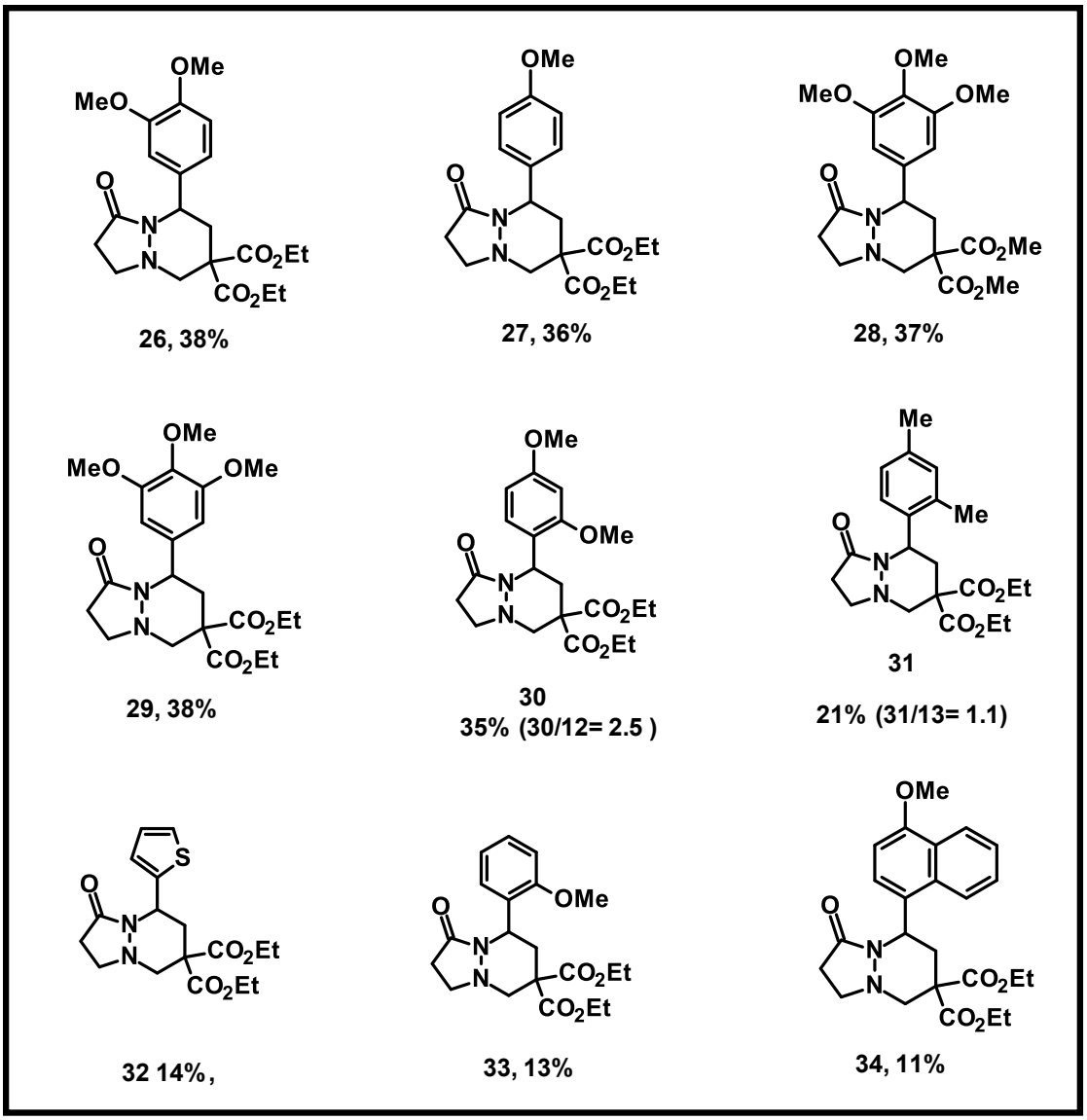
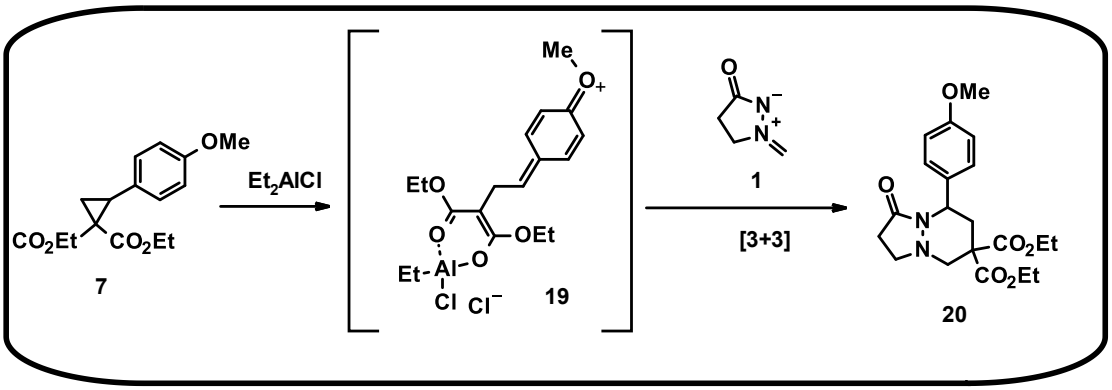


Table 3: 5,6-fused *N,N*-bridge bicyclic compounds



Scheme 5: Mechanism of the [3+3] cycloaddition reactions of azomethine imine with donor-acceptor cyclopropanes

1.8: Conclusion

We have developed a Lewis acid promoted regioselective [3+2] and [3+3] cycloaddition reactions of donor–acceptor cyclopropanes with a pyrazolidinone azomethine imine to form novel and unprecedented 5,5-fused *N,N*-bridge bicyclic, 5,6-fused *N,N*-bridge bicyclic compounds and 5,5,5-fused *N,N*-bridge tricyclic compounds in high regioselectivity. The methodology provides an easy access to novel heterocyclic structures and building blocks capable of further derivatization for generating compound libraries, which may help in finding new leads for drug discovery and agrochemicals.

Chapter 2

Development of Novel Methodologies for the Synthesis of Functionalized Isoxazolines

2.1: Introduction and brief review of Isoxazole and Isoxazoline and its applications

Chapter 2.1 deals with a brief review on isoxazoles and isoxazolines and their applications.

Isoxazoles and Isoxazoline derivatives are considered as an important family of five-membered heterocyclic compounds, prevalent in wide range of natural products (Calafianin)[19] and diverse biologically active compounds such as Cloxacillin (antibiotic),[20] Acivicin (anti-cancer),[21] Fenoxazulfone (herbicide),[23] Pyroxasulfone (herbicide),[24] and Fluralaner (insecticide and acaricide)[25] (**Figure 2**). These compounds display broad spectrum of application in several areas of chemical industry like pharmaceuticals,[26] dyes,[27] organocatalysts,[28] organic synthesis [29] and agrochemicals.[30,31]

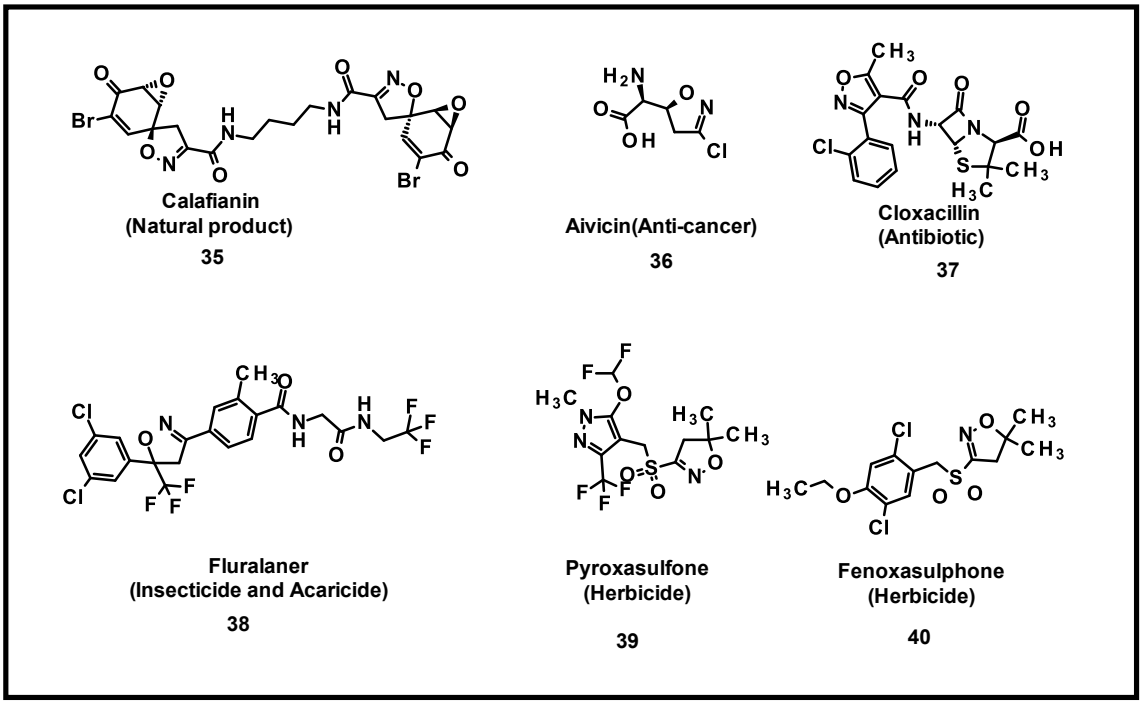


Figure 4: Biologically active *N,N*-bridged heterocycles

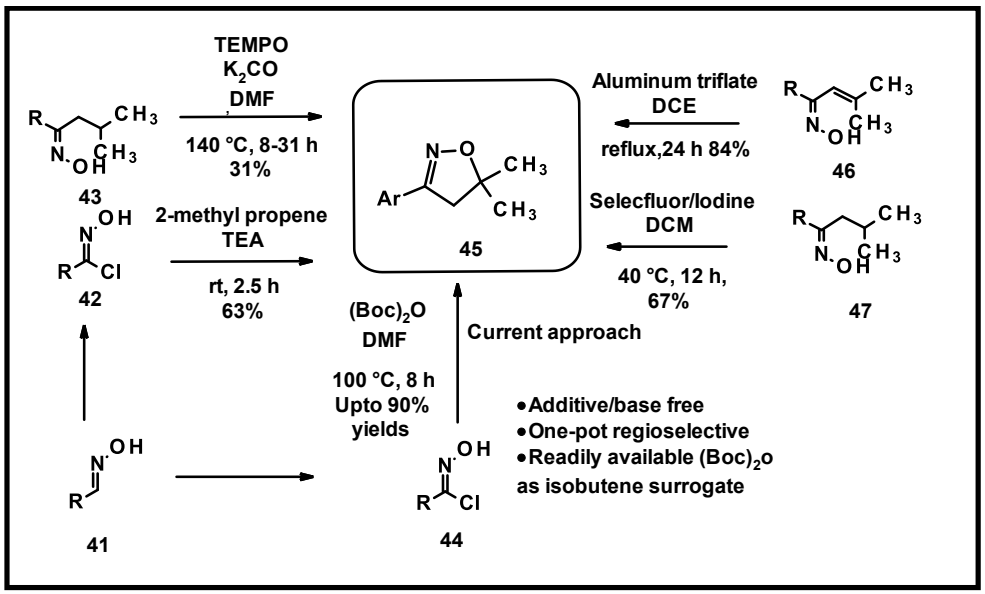
2.2: Methods to synthesize isoxazole derivatives

Chapter 2.2 deals with brief review of methods available in the literature to synthesize isoxazole and isoxazoline derivatives.

Various synthetic methods are available in the literature for synthesis of isoxazoles such as 1,3-dipolar cycloaddition of nitrile oxides,[32] condensation of hydroxylamine with 1,3-dicarbonyl compounds and others.[33] First general and popular method for the synthesis of isoxazole derivatives was reported by Quilico, proceeded *via* [3+2] cycloaddition reaction between nitrile oxides and alkynes.[34] For many years, this was the method of choice to prepare isoxazoles and isoxazolines. Metal-catalyzed isoxazole synthesis was also reported by Fokin and co-workers in 2005[35]. The [3+2] cycloaddition approach is still considered as the convenient route and this strategy was extensively utilized for the preparation of isoxazole derivatives.[36]

2.3: Methods to synthesize 5,5-Dimethyl isoxazoline compounds

Chapter 2.3 deals with the methods available in literature to synthesize isoxazole derivatives. Dimethyl isoxazolines are versatile scaffolds for the synthesis of complex natural products and found in bioactive compounds (Pyroxasulfone and Fluralaner) (**Figure-2**). These have also been employed for the synthesis of oxetanes and cyclobutanes *via* intermolecular aza Paternò–Büchi reactions in the recent past.[35] There are few reports available for the synthesis of 5,5-dimethyl isoxazolines. Shunsuke Chiba and co-workers reported TEMPO-mediated 5,5-dimethyl-3-phenyl-4*H*-isoxazoline synthesis from 3-methyl-1-phenyl-butan-1-one oxime with 33% yield.[36] Feng Liu and co-workers described 5,5-dimethyl isoxazole synthesis using Selectfluor–Bu_4NI as a catalyst with 67% yield.[37] Elisabet Dunach and co-workers documented aluminium (III) triflate mediated 5,5-dimethyl isoxazole synthesis from oximes with 84% yield.[38] Corinna S. Schindler and co-workers reported 1,3-dipolar cycloadditions of nitrile oxides with isobutene to afford isoxazole derivatives in good yield.[39] There are some other methods also available for 5,5-dimethyl isoxazole synthesis.[40] All the above methods suffer from several limitations such as low yield, requirement of expensive catalysts, oxidizing agents or bases.



Scheme 6: Methods to synthesize 5,5-dimethyl isoxazoline compounds

2.4: Research objective.

Chapter 2.4 deals with the research objective.

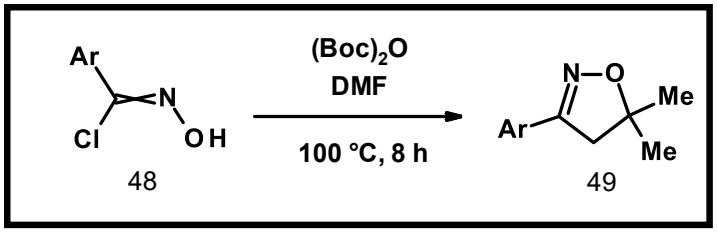
To address the limitations, novel and advance of effective methodologies are essential to synthesize 5,5-dimethyl isooxazoline. In this background, the present research work has been aimed to develop novel routes to synthesize 5,5-dimethyl isooxazoline. we aim to explore the additive free synthesis of 5,5-dimethyl isooxazoline using chloroxime (as a precursor of nitrile oxide dipole) and boc-anhydride (as a surrogate source of isobutene dienophile). This protocol enables the synthesis of functionalized isooxazolines in a highly efficient, base-free, metal free and additive manner.

2.5: Novel methodology to synthesize 5,5-dimethyl isoxazoline derivatives

Chapter 2.5 deals with novel methodology to synthesize 5,5-dimethyl isoxazoline compounds.

We aimed to explore the additive-free synthesis of 5,5-dimethyl isooxazoline using chloroxime (as a precursor of nitrile oxide dipole) and boc-anhydride(as a surrogate source of isobutene dienophile). This protocol enables the synthesis of functionalized isooxazolines in a highly efficient, base-free, metal free and additive manner

To address the limitations, we aim to explore the additive-free synthesis of 5,5-dimethyl isoxazoline using chloroxime **48** (as a precursor of nitrile oxide dipole) and boc-anhydride (as a surrogate source of isobutene dienophile). This protocol enables the synthesis of functionalized isoxazolines in a highly efficient, base-free, metal-free and additive-free manner.



Scheme 7: [3+2] cycloaddition reactions of chloroxime and Boc anhydride

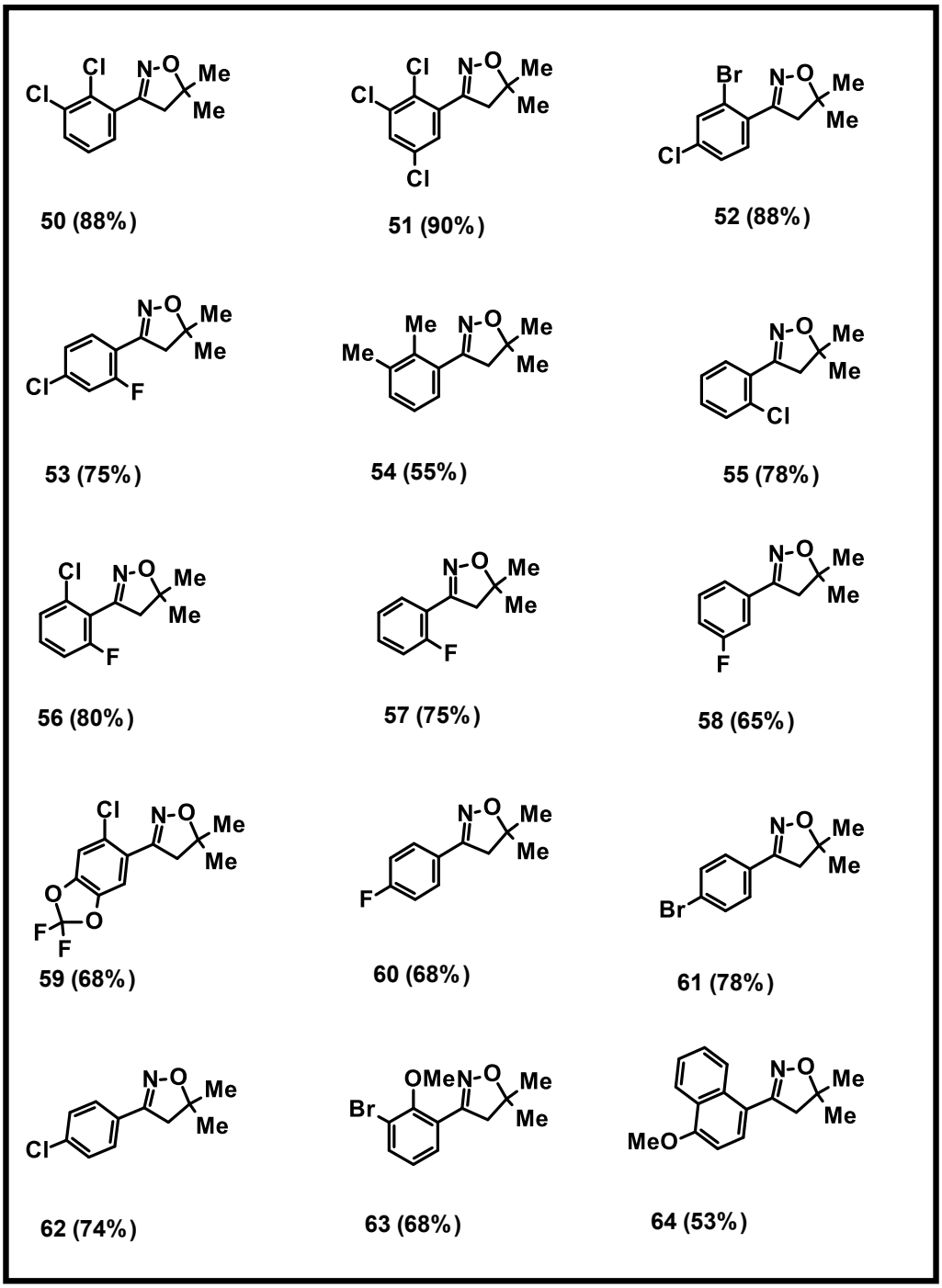


Table 4: Isoxazoline derivatives *via* [3+2] cycloaddition reactions

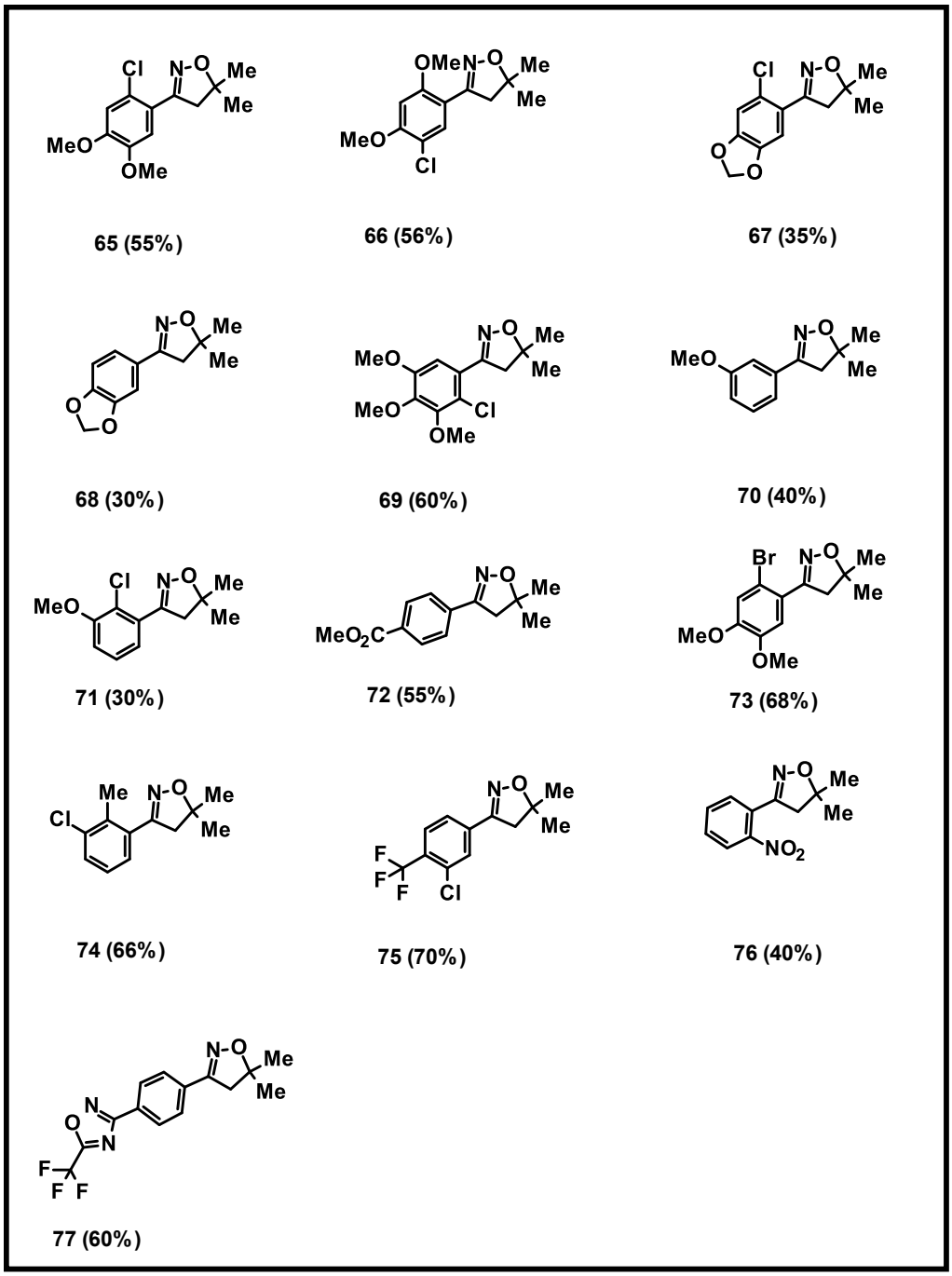
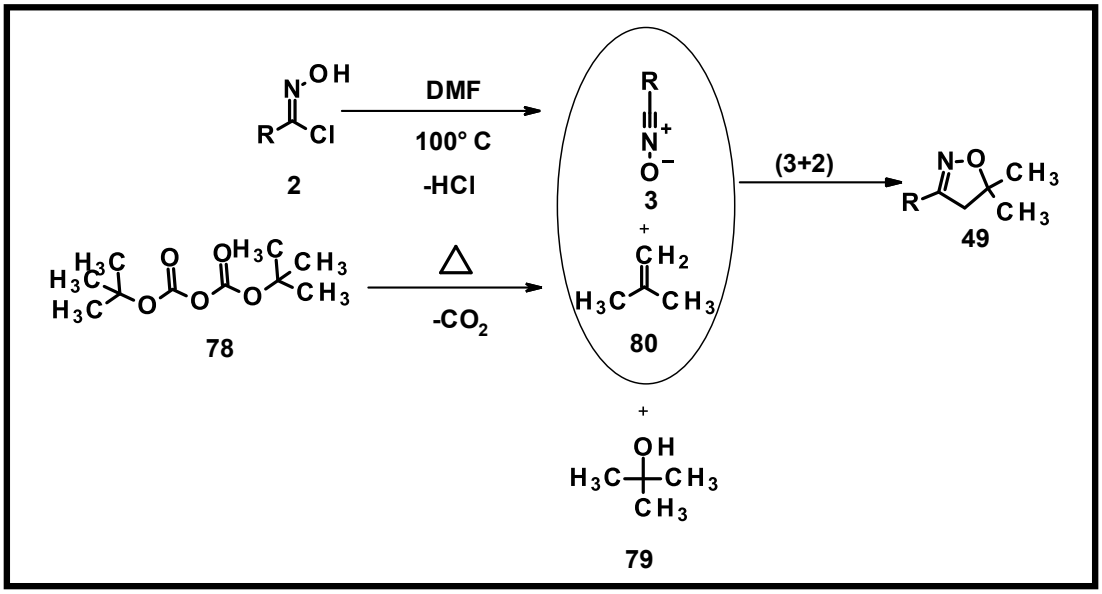


Table 5: Isoxazoline derivatives *via* [3+2] cycloaddition reactions



Scheme 8: Mechanism of the [3+2] cycloaddition reaction of nitrile oxide and isobutene 5,5-dimethyl isoxazoline

2.6: Novel methodology to synthesize 5,5-Dimethyl isooxazoline derivatives

Section seven deals with screening of different conditions and methods for the synthesis of 5,5-dimethyl isooxazoline.

2.7: Synthesis of 5,5-dimethyl isoxazoline *via* flow chemistry

We have synthesized 5,5-dimethyl isoxazoline from chloroxime (as a precursor of nitrile oxide dipole) and boc-anhydride (a surrogate source of isobutene dienophile) *via* conventional method. But this reaction could be challenging if the scale of the reaction is increased. There could be safety and operational issues that may arise at a large scale in conventional methods. Herein, we aimed to synthesize 5, 5-dimethyl isoxazolines under flow conditions.

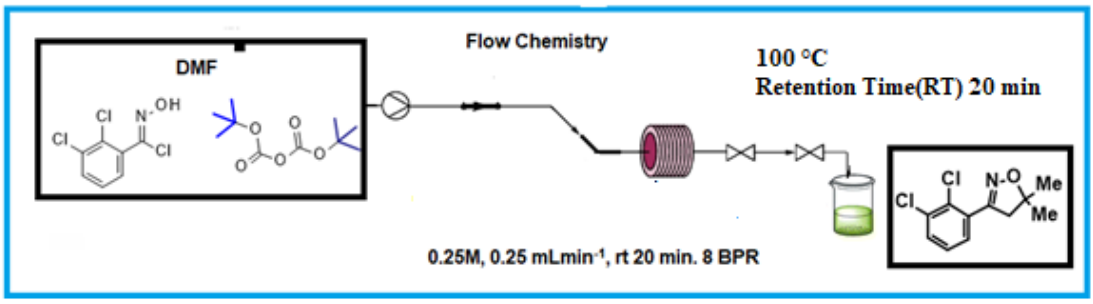


Figure 5: [3+2] Cycloaddition reactions of chloroxime and Boc anhydride in a flow reactor

The high temperature was easily obtained compared to a batch reactor. The time-temperature profile can be easily reproduced regardless of material requirements. The reaction mixture quickly reaches temperature upon entering the high-temperature zone and quickly cools after leaving the high-temperature zone. This allows better control over side reactions (such as product decomposition in this case). This process allowed us to make it in a short time while mitigating the potential chemical hazards and safety was also enhanced.

2.8: Conclusion

we have developed a one-pot regioselective synthesis of isoxazolines from nitrile oxide and Boc-anhydride as surrogate source of isobutene with good to moderate yields (40-90%). There was no evidence of any self-condensed nitrile oxide side product in the present method. This method has a clear advantage for the synthesis of dimethyl isoxazolines from easily available starting materials like chloroxime and boc anhydride. The methodology provides easy access to novel heterocyclic structures and building blocks which could be useful in drug and agrochemical discovery.

Chapter 3

Biological Evaluation of Newly Synthesized *N,N*-fused Heterocyclic Compounds and Functionalized Isoxazolines in Crop Protection Indications

Chapter three deals with **the** biological evaluation of all the synthesized compounds.

In order to address the demands of the growing global population, it is essential to enhance food production. Unfortunately, farmers experience an average loss of 20 to 30 percent of their crop yield annually due to pests and diseases. Mitigating these losses through effective crop protection measures becomes increasingly crucial. It encompasses various measures such as weed control, pest control, insect control, seed care, and disease control, employing crop protection chemicals such as fungicides, herbicides, and insecticides. Some of the commercial crop protection chemicals Azoxystrobin **83** (fungicides, Pinoxaden **82** (herbicides), and Thiamethoxam **83** (insecticides) structure are depicted below in Figure 2.5.

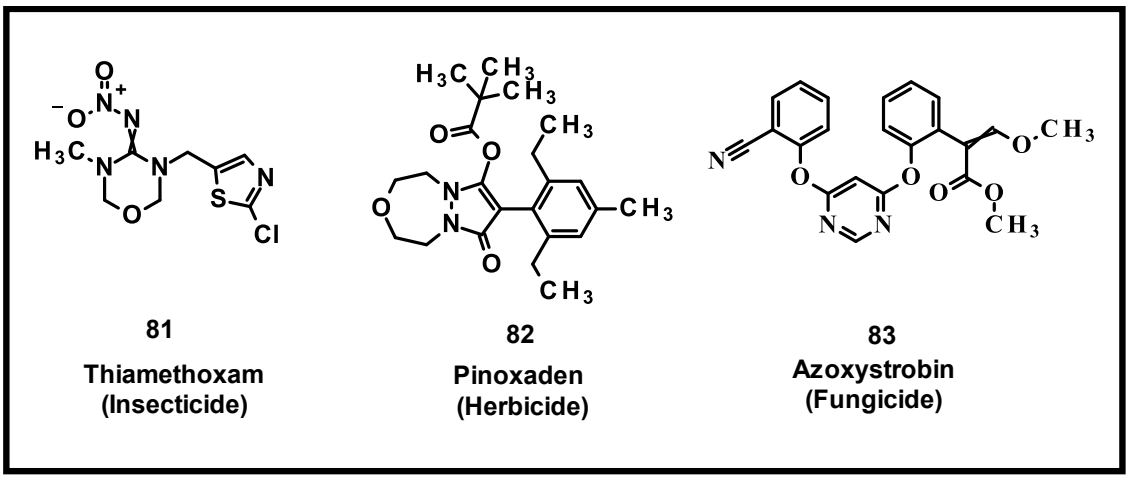


Figure 6: Commercial Crop protection chemicals (fungicides, herbicides, and insecticides

Biological evaluation of all the synthesized compounds (5,5-fused *N,N*-bridge bicyclic compounds, 5,6-fused *N,N*-bridge bicyclic compounds , of 5,5,5-fused *N,N*-bridge tricyclic compounds and 5,5-dimethyl isoxazoline) were screened against all three agrochemical indications (insecticide fungicide and herbicide). Few compounds showed moderate to good herbicidal, insecticide activity, and fungicide activity.

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List of publications

A. National/International Journals.

A] In National/International Journal

"Lewis Acid Mediated [3+2] and [3+3] Annulations of an Azomethine Imine with Donor–Acceptor Cyclopropanes"

Raghuramaiah Mandadapu, Amol Satish Dehadea, Shrikant Abhiman Shetea, Mark Montgomery, Vikas Sikervar*[a] Ravindra Sonawane*[a]

Synthesis **2021**, 53, 2865–2873, DOI: 10.1055/a-1503-8068; Art ID: ss-2021-z0153-op

B. National/International Conference Proceedings.

Poster Titled as "**Additive-Free Efficient and Regioselective Construction of Functionalised Isoxazolines from Chloro-Oxime and Boc-Anhydride"**

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